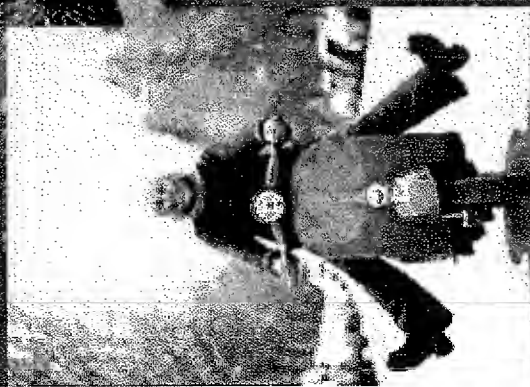


**FemmePharma Global Healthcare, Inc.**

***Delivering the Difference  
in Women's Healthcare***



**FemmePharma**  
GLOBAL HEALTHCARE, INC.



# ***Transdermal vs Mammary vs Topical Delivery***

- **Transdermal Delivery**
  - Through the skin with the intent of systemic delivery
  - Bypass intestinal and hepatic metabolism
  - Usually applied at site remote to target organ



FenmePharma  
A LECHE DISTIBUITION INC.



# ***Transdermal vs Mammary vs Topical Delivery***

- **Mammary Delivery**

- Through the skin with the intent of regional delivery to underlying breast tissue
- Analogous to pulmonary or intranasal administration
- Achieve high regional concentrations for binding at receptors in the breast
- Minimal systemic exposure



FemmetPharma  
A FORTIS VENTURES COMPANY



# ***Transdermal vs Mammary vs Topical Delivery***

- **Topical Dermal Delivery**
  - **Direct application to the skin with the intent of working within the skin itself**
  - **Minimal systemic or regional involvement.**

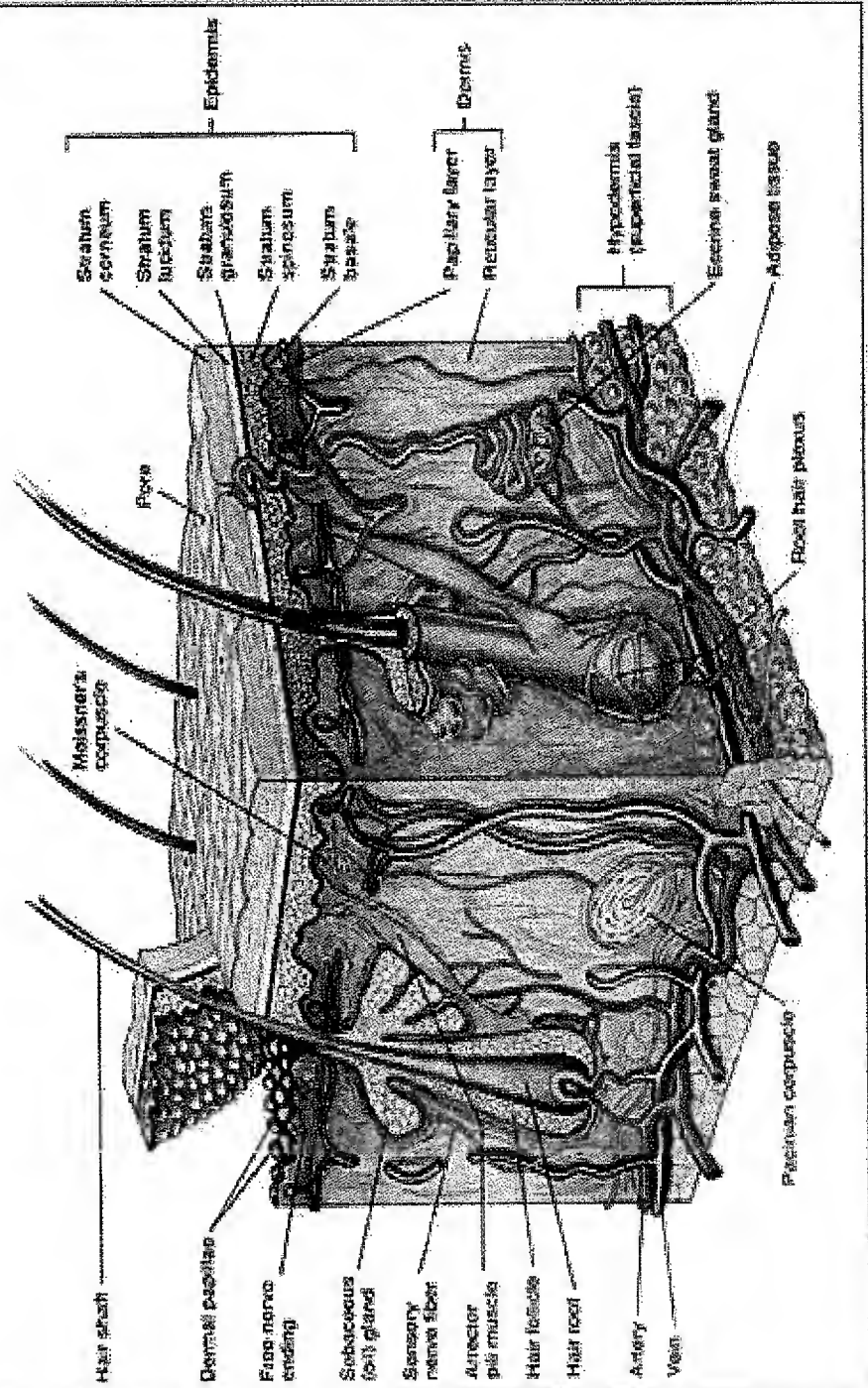


FemmerPharma  
A NEW PHARMACEUTICAL

# Anatomy of Normal Skin

FIGURE 3

Structure of the Skin Membrane





# ***Vaginal Epithelium***

Figure 2

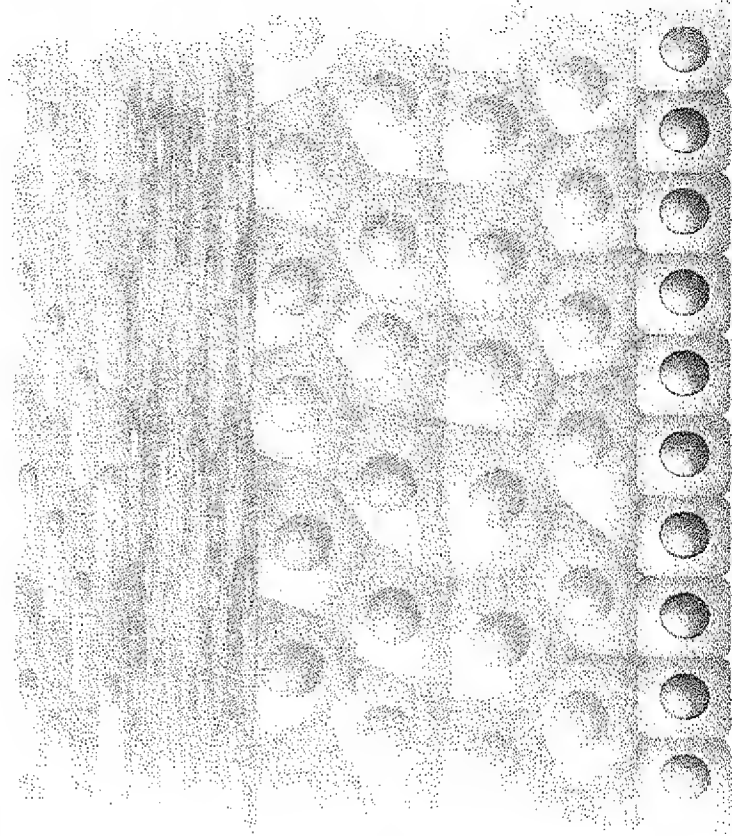
## **The Vaginal Epithelium**

Superficial cells

Intermediate cells

Parabasal cells

Basal cells



*FemmelPharma*  
GmbH & Co. KG

# Epithelial Cell

## Apical plasma membrane

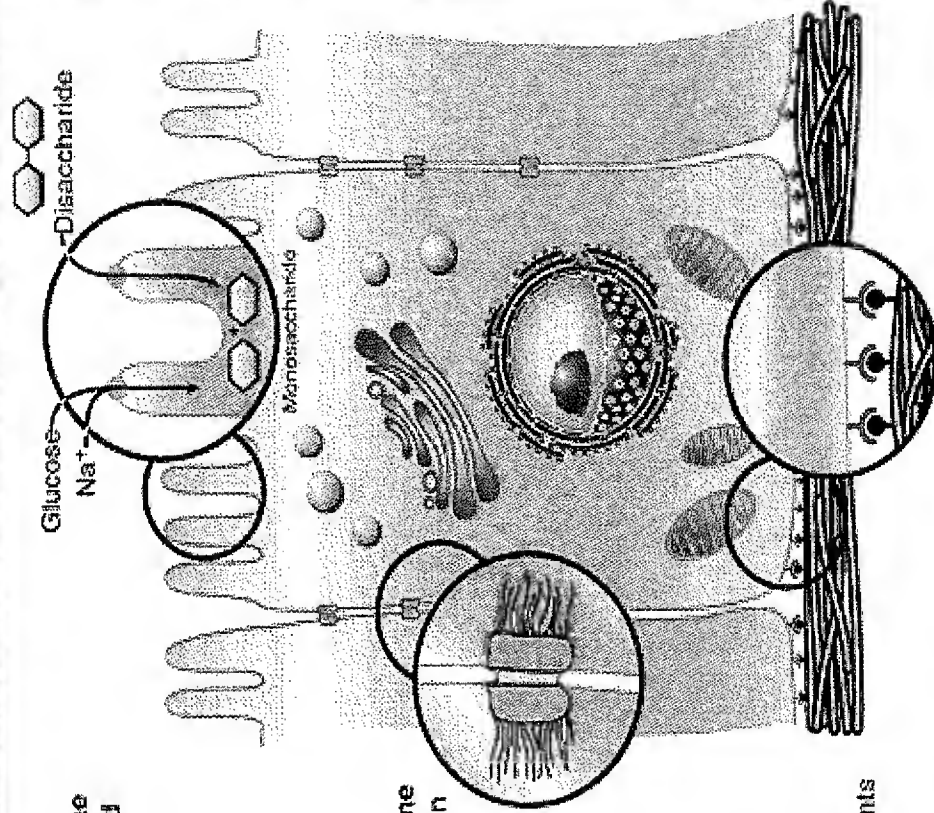
- regulation of nutrient and water intake
- regulated secretion
- protection

## Lateral plasma membrane

- cell contact and adhesion
- cell communication

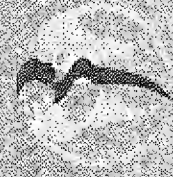
## Basal membrane

- cell-substratum contact
- generation of ion gradients



(a)

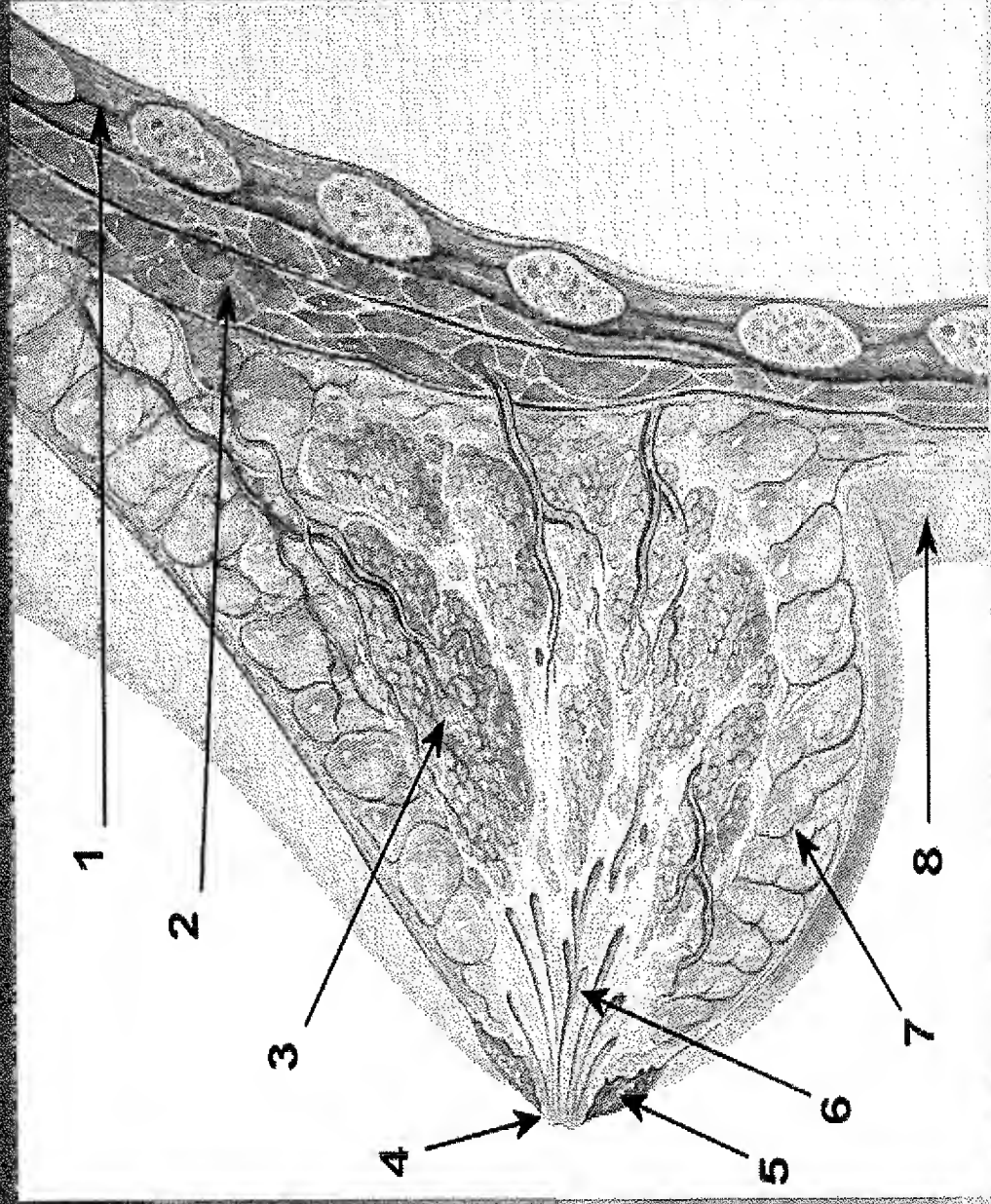
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FemmelPharma  
Cellular and Molecular Biology



# Anatomy of the Female Breast



FemmelPharma  
Produktions- und Vertriebsgesellschaft



# Formulation Comparisons

• Application Site	Breast	Vagina
• Indication	Breast Pain	Endometriosis
• Appearance	Colorless-yellow tinge, <i>clear</i> , semi-lucent	White, <i>opaque</i>
• Properties	Gel with <i>solubilized</i> danazol	Gel with danazol in <i>suspension</i>
• Particle Size	Solution	Micro/nanoparticles
• Excipients	Enhancer/Solubilizing	None
• Danazol		
• Concentration	2% (w/v)	47% (w/w)
• Volume	>1ml/breast	200ul



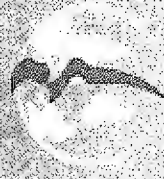
FemmePharma  
VAGINAL INTRACAVITY, INC.



# ***Reviewer's Comments***

## ***WO Application***

- Transdermal for systemic drug administration
- FP contemplates high breast levels with minimal systemic concentrations
- We removed micro and nanoparticles
- Double patenting(5,993,856)-marked differences in formulations gel vs suspension

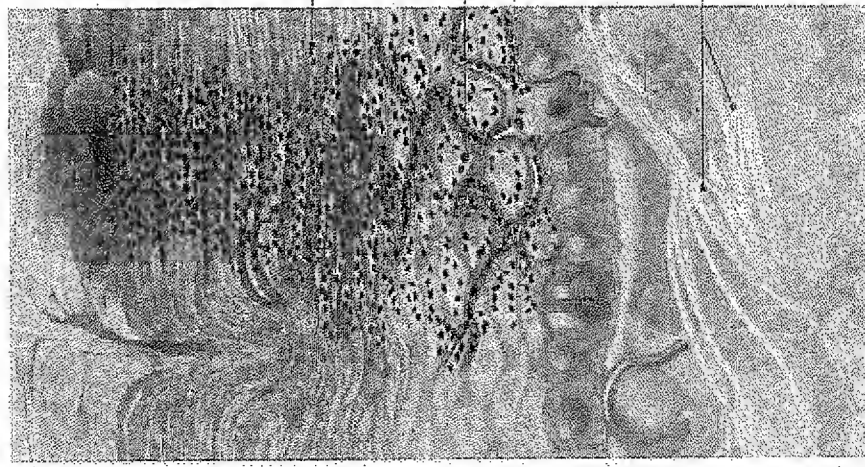


**FemmePharma**  
21-43003, 18-0710-AMC, 18-06



# Sun Induced Damage to Skin

DAMAGED SKIN



EPIDERMIS

DERMIS

stratum corneum is thick and dehydrated

skin cells are misshapen and disorganized

excess melanin causes freckles and age spots

collagen and elastin fibers are weak and damaged

HEALTHY SKIN



stratum corneum is thin and hydrated

new skin cells are healthy and full

corrected pigment cells distribute melanin evenly

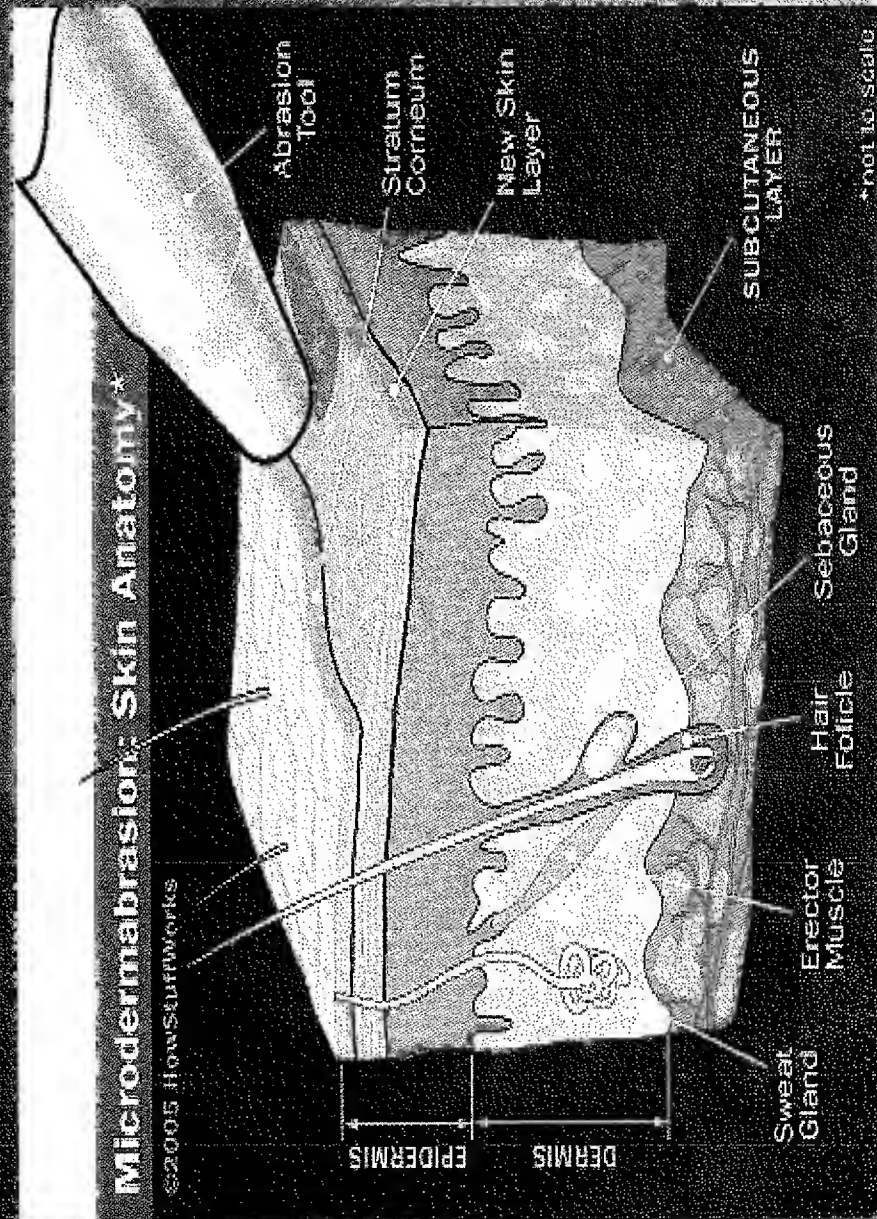
supporting skin structure is strong and resilient



FemmePharma

CLINICAL RESEARCH

# Microabrasion Damage to Skin



FemmePharma  
Cosmetic HealthCare, Inc.



# ***Comparative Pharmacokinetics of Oral and Mammary Applied Danazol***

**Approved oral danazol for FBD 50 to 200  
mg twice daily**

**Oral 200 mg twice daily  
C<sub>max</sub> ~180 ng/ml**

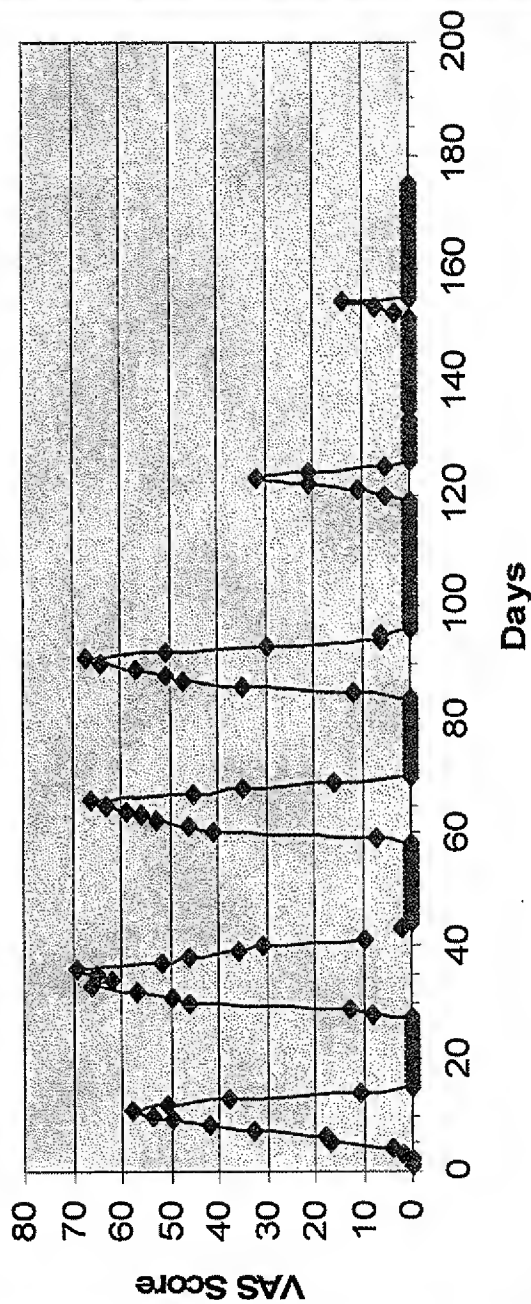
**Danazol Gel 80 mg once daily  
C<sub>max</sub> <2.75 ng/ml**



**FemmePharma**  
A GILSON PHARMACEUTICAL, INC.

# ***Pain Reduction with Danazol Gel in Breast Disease***

Subj. 24/072



Series 1



2/2/2010 Brenda Frazier, Jennifer Kim Family  
PP, AR  
GenD: Pianos Peter Mayer, John Zenniah

GD discussed Company & its woman-oriented focus

areas of interest: endometriosis

urinary incontinence - phase III

fibrocystic breast disease

Phase IIb clinical trial

for pain associated w/ fibrocystic breast disease

danazole administered systemically has significant androgenic side effects

no other treatment

affects 26M women in US

no systemic side effects in clinical trial  
still looking at dose

12 - WO 00/72883

into skin not transdermal

particle are not dissolved into by

doses are different  
purpose is different

hydrogel - water + viscosity modifier + crystalline structure  
hydroalcoholic - water + alcohol + penetration enhancer

Rec'd for Docketing on:

JAN 10 2010

Docketed by GJG on 2-18-10

Given to TJB on 2-18-10

(2)

2/2/2010

12 - danazol is not soluble in water  
OD - danazole could be administered

Rapavan - PVP

PM - 2-pyrrolidini

N-methyl-2-pyrrolidini

Comparison to literature

No transdermal penetration to breast



## Amendment

### In the claims

1. (currently amended) A drug formulation comprising  
~~a drug selected from the group consisting danazol[[,]] bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues in an amount effective to provide regional~~  
providing regionally effective, not systemic systemically effective, levels of danazole when  
administered transdermally to the breast, to provide relief from benign diseases or disorders of  
the breast,

wherein the danazole is formulated in a hydroalcoholic gel pharmaceutical carrier  
~~comprising a transdermal penetration enhancer in which the danazol is soluble to enable promote~~  
in an effective amount to deliver  
delivery of the drug danazol across the stratum corneum to the breast tissue.

2.-9. (cancelled)

10. (withdrawn, currently amended) A method for treating a disease or disorder of the  
treatable with danazol  
breast, comprising

topically administering to the breast of a patient,

*Same limit*  
a drug formulation suitable for local or regional delivery comprising an effective amount  
of drug selected from the group consisting of danazol[[,]] bromocriptine, and luteinizing  
hormone-releasing hormone (LHRH) analogues,

in an amount ~~effective to provide regional~~ providing regionally effective, not systemic  
systemically effective, levels of danazole when administered transdermally to the breast, to  
provide relief from benign diseases or disorders of the breast,

wherein the danazole is formulated in a hydroalcoholic gel pharmaceutical carrier  
comprising a transdermal penetration enhancer in which the danazol is soluble to enable promote  
delivery of ~~the drug~~ danazol across the stratum corneum to the breast tissue.

11-16. (cancelled)

17. (withdrawn, previously presented) The method of claim 10 wherein the benign  
disease of the breast is selected from the group consisting of mastalgia, mastodynia, ~~Mondor's~~  
~~disease~~, fibrocystic breast disease, costochondritis, mastitis, ~~Paget's disease of the areola~~,  
fibroadenoma, ~~breast abscess~~, and ~~breast infections~~.

18. (cancelled)

19. (withdrawn, previously presented) The method of claim 10 wherein the region is the  
breast, areola, and underlying musculature of the chest.